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EDUCATION

1975	B.S. Chemistry, Queens College, Flushing, NY
1980	M.Phil. Chemistry, City University of New York, New York, NY
1981	Ph.D. Organic Chemistry, City University of New York, New York, NY
1981-1985	Postdoctoral, Organic Synthesis, Professor Herbert O. House, Georgia Institute of Technology, Atlanta, GA

BACKGROUND

3/95 - Present	Scientist, Chemical Synthesis and Analysis Laboratory, SAIC Frederick, NCI-Frederick Cancer Research and Development Center, Frederick, MD
1985 - 3/95	Scientist, Chemical Synthesis and Analysis Laboratory, Program Resources, Inc., NCI-Frederick Cancer Research and Development Center, Frederick, MD
1981- 1985	Postdoctoral Fellow, Organic Synthesis, Professor Herbert O. House, Georgia Institute of Technology, Atlanta, GA
1976 - 1981	Graduate Fellow, Department of Chemistry, Queens College, New York, NY
1975 - 1976	Teaching Assistant, Department of Chemistry, Queens College, New York, NY
1975	Research Associate, Natural Products Chemistry, Queens College, New York, NY

PUBLICATIONS

Berkowitz, W.F., Sasson, I., Sampathkumar, P.S., Hrabie, J.A., Choudhry, S.C. and Pierce, D. Chiral postanoid intermediates from aucubin. Tet. Lett., 1979, 1641-1644, 1979.

Berkowitz, W.F., Choudhry, S.C. and Hrabie, J.A. The conversion of asperuloside to optically active prostaglandin intermediates. J. Org. Chem., 47, 824-829, 1982.

House, H.O., Hrabie, J.A. and Narasimhan, S.L. Synthesis of certain cyclic silanes. J. Chem. Eng. Data, 31, 124-127, 1986.

JOSEPH A. HRABIE, Ph.D. PUBLICATIONS (cont'd)

House, H.O., Hrabie, J.A. and VanDerveer, D. Unsymmetrically substituted 1,8-diarylanthracenes. J. Org. Chem., 51, 921-929, 1986.

Wade, D., Yang, C.S., Metral, C.J., Roman, J.M., Hrabie, J.A., Riggs, C.W., Anjo, T., Keefer, L.K. and Mico, B.A. Deuterium isotope effect on denitrosation and demethylation of N-nitrosodimethylamine by rat liver microsomes. Cancer Research, 47, 3373-3377, 1987.

Keefer, L.K., Hrabie, J.A. Ohannesian, L., Flippen-Anderson, J.L. and George, C. A symmetrically hydrogen-bonded binitrosamine cation produced on protonation of N-nitrosopyrrolidine. J. Amer. Chem. Soc., 110, 3701-3702, 1988.

Keefer, L.K. Hrabie, J.A., Hilton, B.D. and Wilbur, D. Nitrogen protonation of N-nitrosodimethylamine. J. Amer. Chem. Soc., 110, 7459-7462, 1988.

Keefer, L.K., Ohannesian, L. and Hrabie, J.A. Isolation of stable 1:1 and 2:1 salts of nitrosamines with protic acids. J. Org. Chem., 54, 2432-2436, 1989.

Streeter, A.J., Nims, R.W., Hrabie, J.A., Heur, Y.-H. and Keefer, L.K. Sex differences in the single dose toxicokinetics of N-nitrosomethyl(2-hydroxyethyl)amine in the rat. Cancer Res., 49, 1783-1789, 1989.

Streeter, A.J., Sheffels, P.R., Hrabie, J.A., Ohannesian L., Heur, Y.-H., Mico, B.A. and Keefer, L.K. Deuterium isotope effect on the toxicokinetics of monomethylamine in the rat. Drug Metab. Dispos., 18, 447-452, 1990.

Keefer, L.K., Kroeger-Koepke, M.B., Ishizaki, H., Michejda, C.J., Saavedra, J.E., Hrabie, J.A., Yang, C.S. and Roller, P.P. Stereoselectivity in the microsomal conversion of N-nitrosodimethylamine to formaldehyde. Chem. Rsch. Toxicology, 3, 540-544, 1990.

Maragos, C.M., Morley, D., Wink, D.A., Dunams, T.M., Saavedra, J.E., Hoffman, A., Bove, A.A., Issac, L., Hrabie, J.A. and Keefer, L.K. Complexes of 'NO with nucleophiles as agents for the controlled biological release of nitric oxide. Vasorelaxant effects. J. Med. Chem., 34, 3242-3247, 1991.

Diwan, B.A., Lubet, R.A., Ward, J.M., Hrabie, J.A. and Rice, J.M. Tumor promoting and hepatocarcinogenic effects of 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene (TCPOBOP) in DBA/2NC4 and C57BL/6NC4 mice and F344/NC4 rats initiated with N-nitrosodiethylamine. Carcinogenesis, 113, 1893-1902, 1992.

Maragos, C.M., Wang, J.M., Hrabie, J.A. Oppenheim, J.J. and Keefer, L.K. Nitric oxide/nucleophile complexes inhibit the in vitro proliferation of A375 melanoma cells via nitric oxide release. Cancer Res., 53, 564-568, 1993.

JOSEPH A. HRABIE, Ph.D. PUBLICATIONS (cont'd)

Hrabie, J.A., Klose, J.R., Wink, D.A. and Keefer, L.K. New nitric oxide-releasing zwitterions derived from polyamines. J. Org. Chem., 58, 1472-1476, 1993.

Keefer, L.K., Christodoulou, D., Dunams, T.M., Hrabie, J.A., Maragos, C.M., Saavedra, J.E. and Wink, D.A. Chemistry of the "NONOates", unusual *N*-nitroso compounds formed by reacting nitric oxide with nucleophiles. ACS Symposium Series, 553, 136-146, 1994.

Smith, D.J., Chakravarthy, D., Pulfer, S., Simmons, M.L., Hrabie, J.A., Citro, M.L., Saavedra, J.E., Davies, K.M., Hutsell, T.C., Mooradian, D.L., Hanson, S.R. and Keefer, L.K. Nitric oxide-releasing polymers containing the [N(O)NO] group. J. Med. Chem., 39, 1148-1156, 1996.

Hrabie, J.A., Srinivasan, A., George, C. and Keefer, L.K. Reaction of nitric oxide with the imine double bond of certain Schiff bases. Tetrahedron Lett., 39, 5933-5936, 1998.

Stoll, H.-P., Carlson, K., Keefer, L.K., Hrabie, J.A. and March, K.L. Pharmacokinetics and consistency of pericardial delivery directed to coronary arteries: Direct comparison with endoluminal delivery. Clin. Cardiol., 22 (Suppl. I), I10-I16, 1999.

Jeong, M.H., Marks, D.S., Keefer, L.K., Hrabie, J.A., Southan, G.J., Stewart, M.L., Lerman, A., Gegoire, J., Staub, M.E., Holmes, D.R. and Schwartz, R.S. Local nitric oxide delivery using a novel donor markedly limits arterial platelet deposition and occlusion following severe injury. Circulation, in press, 1999.

Hrabie, J.A., Saavedra, J.E., Davies, K.M. and Keefer, L.K. Adducts of piperazine with nitric oxide. Org. Prep. Proced. Int., 31, in press, 1999.

BOOK CHAPTER

Hrabie, J.A. and Keefer, L.K. Nitric oxide donors. In *The Pathophysiology and Clinical Applications of Nitric Oxide*, edited by G.M. Rubanyi, Chapter 25. London: Harwood Academic, in press, 1999.

PATENTS

Berkowitz, W.F. Choudhry, S.C. and Hrabie, J.A. Conversion of Iridoids to Prostaglandins. U.S. Patent No. 4,410,710. Issued October 18, 1983.

Keefer, L.K., Hrabie, J.A., Wink, D.A. and Dunams, T.M. Stabilized Nitric Oxide - Primary Amine Complexes Useful as Cardiovascular Agents. U.S. Patent No. 4,954,526. Issued September 4, 1990.

JOSEPH A. HRABIE, Ph.D. PATENTS (cont'd)

Dunams, T.M., Hrabie, J.A., Keefer, L.K. and Wink, D.A. Antihypertensive Compositions of Secondary Amine-Nitric Oxide Adducts and Use Thereof. U.S. Patent No. 5,039,705. Issued August 13, 1991.

Hrabie, J.A. and Keefer, L.K. Complexes of Nitric Oxide with Polyamines. U.S. Patent No. 5,155,137. Issued October 13, 1992.

Dunams, T.M., Hrabie, J.A., Keefer, L.K. and Wink, D.A. Antihypertensive Compositions of Secondary Amine-Nitric Oxide Adducts and Use Thereof. U.S. Patent No. 5,208,233. Issued May 4, 1993.

Dunams, T.M., Hrabie, J.A., Keefer, L.K. and Wink, D.A. Antihypertensive Compositions and Use Thereof. U.S. Patent No. 5,212,204. Issued May 18, 1993.

Hrabie, J.A. and Keefer, L.K. Complexes of Nitric Oxide with Polyamines. U.S. Patent No. 5,250,550. Issued October 5, 1993.

Keefer, L.K., Hrabie, J.A., Wink, D.A. and Dunams, T.M. Stabilized Nitric Oxide - Primary Amine Complexes Useful as Cardiovascular Agents. European Patent No. 495,776. Issued February 1, 1995.

Hrabie, J.A. and Keefer, L.K. Polymer-Bound Nitric Oxide/Nucleophile Adduct Compositions, Pharmaceutical Compositions Incorporating Same and Methods of Treating Biological Disorders Using Same. U.S. Patent No. 5,405,919. Issued April 11, 1995.

Dunams, T.M., Hrabie, J.A., Keefer, L.K. and Wink, D.A. Pharmaceutical Compositions of Secondary Amine-Nitric Oxide Adducts. U.S. Patent Application No. 08/476,601. Filed June 6, 1995.

Hrabie, J.A., Saavedra, J.E. and Keefer, L.K. Polymer-Bound Nitric Oxide/Nucleophile Adduct Compositions, Pharmaceutical Compositions Incorporating Same and Methods of Treating Biological Disorders Using Same. U.S. Patent No. 5,525,357. Issued June 11, 1996.

Keefer, L.K. and Hrabie, J.A. Implants, Prostheses, and Stents Comprising Polymer-Bound Nitric Oxide/Nucleophile Adducts Capable of Releasing Nitric Oxide. U.S. Patent No. 5,676,963. Issued October 14, 1997.

Hrabie, J.A. and Keefer, L.K. Method of Generating Nitric Oxide Gas Using Nitric Oxide Complexes. U.S. Patent No. 5,683,668. Issued November 4, 1997.

JOSEPH A. HRABIE, Ph.D. PATENTS (cont'd)

Hrabie, J.A. and Keefer, L.K. Polymer-Bound Nitric Oxide/Nucleophile Adduct Compositions, Pharmaceutical Compositions Incorporating Same and Methods of Treating Biological Disorders Using Same. U.S. Patent No. 5,718,892. Issued February 17, 1998.

Keefer, L.K., Saavedra, J.E. and Hrabie, J.A. N-Substituted Piperazine Nonoates. U.S. Patent No. 5,721,365. Issued February 24, 1998.

Keefer, L.K., Wink, D.A., Dunams, T.M. and Hrabie, J.A. Anti-hypertension Compositions of Secondary Amine-Nitric Oxide Adducts and Use Thereof. U.S. Patent No. 5,731,305. Issued March 24, 1998.

Hrabie, J.A. and Keefer, L.K. Novel Nitric Oxide-Releasing Amidine- and Enamine-Derived Diazenium diolates, Compositions and Uses Thereof and Method of Making Same. U.S. Patent Application No. 60/051,690. Filed July 3, 1997. PCT Filed July 2, 1998.

MEETING ABSTRACTS

Streeter, A.J., Nims, R.W., Hrabie, J.A., Heur, Y.-H. and Keefer, L.K. Toxicokinetics of *N*-nitrosomethyl(2-hydroxyethyl)amine in the rat. Presented to the 27th Annual Meeting of the Society of Toxicology, Dallas, Texas, February 17, 1988.

Hrabie, J.A., Streeter, A.J., Nims, R.W. and Keefer, L.K. Single dose toxicokinetics of NMHA in rats. Presented to the Eppley Institute Symposium on Advances in the Biology and Chemistry of *N*-Nitroso and Related Compounds, Omaha, Nebraska, May 22, 1988.

Morley, D., Vosacek, R., Keefer, L.K., Bove, A.A., Maragos, C., Wink, D., Dunams, T.M. and Hrabie, J.A. Vasorelaxant potency of diethylamine/nitric oxide adduct is similar to traditional nitrates. Presented to the 1991 FASEB National Meeting, Atlanta, Georgia, April 18, 1991.

Hrabie, J.A., Dunams, T.M., Maragos, C.M., Keefer, L.K., Wink, D.A., Bove, A.A. and Morley, D. Complexes of NO with nucleophiles as agents for the controlled biological release of nitric oxide. Vasorelaxant effects. Presented to the 201st National Meeting of the American Chemical Society, Atlanta, Georgia, April 16, 1991.

Morley, D., Maragos, C., Keefer, L.K., Wink, D. and Hrabie, J.A. Nucleophile-nitric oxide adducts spontaneously release nitric oxide and have vasodilator potency equivalent to glyceryl trinitrate and nitroprusside. Presented to the 64th Scientific Sessions of the American Heart Association, Anaheim, California, November 11, 1991.

JOSEPH A. HRABIE, Ph.D. MEETING ABSTRACTS (cont'd)

- Maragos, C.M., Wang, J.M., Hrabie, J.A., Oppenheim, J.J. and Keefer, L.K. Nitric oxide/nucleophile complexes inhibit the proliferation of A375 melanoma cells via nitric oxide release. Presented to the National Meeting of the American Association for Cancer Research, San Diego, California, May 20, 1992.
- Hrabie, J.A., Dunams, T.M., Christodoulou, D., Maragos, C.M., Saavedra, J.E. and Keefer, L.K. Chemistry and biochemistry of the "NONOates", *N*-nitroso compounds formed by reacting nitric oxide with nucleophiles. Presented to the 204th National Meeting of the American Chemical Society, Washington, DC, August 25, 1992.
- Keefer, L.K., Christodoulou, D., Davies, K.M., Hrabie, J.A., Saavedra, J.E., Southan, G.J. and Srinivasan, A. New nitric oxide-releasing diazeniumdiolate preparations useful for biomedical applications. Presented to the International Conference on the Biochemistry and Molecular Biology of Nitric Oxide, UCLA, Los Angeles, California, July 14, 1996.
- Hrabie, J.A., Keefer, L.K., Saavedra, J.E. Discovery of new nitric oxide-releasing drugs and their biomedical applications. Presented at the First Annual NCI-FCRDC Spring Research Festival, Frederick, Maryland, May 21, 1997.
- Baek, S.H., Stoll, H.-P., Szabo, A., Keefer, L.K., Hrabie, J.A. and March, K.L. Pharmacokinetics of agent distribution from the pericardial space: Effects of agent size and validation of a mathematical model for epicardial penetration. Presented to the 47th Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, March 23, 1998.
- Shanklin, A.P., Buzard, G.S., Davies, K.M., Fitzhugh, A.L., Hrabie, J.A., Keefer, L.K. and Saavedra, J.E. Nitric oxide-releasing diazenium diolates: From basic research to promising drug discovery opportunities. Presented at the NIH Research Festival '98, Bethesda, Maryland, October 8, 1998.
- Keefer, L.K., Srinivasan, A., Saavedra, J.E., Toscano, J., Davies, K.M. and Hrabie, J.A. Diazenium diolates: Interrelationships with more traditional *N*-nitroso compounds. Presented to the 217th National Meeting of the American Chemical Society, Anaheim, California, March, 1999.
- Hrabie, J.A., Saavedra, J.E. and Keefer, L.K. Nitric oxide-releasing derivatives of proteins and other biomedically important substrates. Presented at the National Meeting of the American Association for Cancer Research, Philadelphia, Pennsylvania, April, 1999.